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TITLE: Methods, systems, and associated implantable devices for dynamic monitoring of physiological and biological properties of tumors

Abstract Text (1):
Methods of monitoring and evaluating the status of a tumor undergoing treatment includes monitoring in vivo at least one physiological parameter associated with a tumor in a subject undergoing treatment, transmitting data from an in situ located sensor to a receiver external of the subject, analyzing the transmitted data, repeating the monitoring and transmitting steps at sequential points in time and evaluating a treatment strategy. The method provides dynamic tracking of the monitored parameters over time. The method can also include identifying in a substantially real time manner when conditions are favorable for treatment and when conditions are unfavorable for treatment and can verify or quantify how much of a known drug dose or radiation dose was actually received at the tumor. The method can include remote transmission from a non-clinical site to allow oversight of the tumor's condition even during non-active treatment periods (in between active treatments). The disclosure also includes monitoring systems with in situ in vivo biocompatible sensors and telemetry based operations and related computer program products.

Brief Summary Text (9):
In addition, over time, tumors progress through periods wherein they are less robust and, thus, potentially more susceptible to treatment by radiation or drug therapy. Providing a monitoring system which can continuously or semi-continuously monitor and potentially identify such a susceptible condition could provide welcome increases in tumor destruction rates. Further, especially for regionally targeted tumor treatment therapies, it can be difficult to ascertain whether the desired dose was received at the tumor site, and if so received, it can be difficult to assess its efficacy in a relatively non-invasive manner. Thus, there is a need for a monitoring system which can quantify and/or assess the localized or regional presence of a target drug.

Brief Summary Text (12):
In the past, various biotelemetry devices and implantable sensors have been proposed to monitor cardiac conditions or physiological parameters associated with glucose or temperature. For example, U.S. Pat. No. 5,791,344 to Schulman et al. entitled "Patient Monitoring System," proposes a system to monitor the concentration of a substance in a subject's blood wherein one enzymatic sensor is inserted into a patient to monitor glucose and then deliver insulin in response thereto. Similarly, PCT US98 05965 to Schulman et al, entitled "System of Implantable Devices for Monitoring or Affecting Body Parameters," proposes using microsensors and/or microstimulators to sense glucose level, O.sub.2 content, temperature, etc. There are also a number of implantable medical devices and systems which monitor physiological data associated with the heart via telemetry. One example of this type of device is described in U.S. Pat. No. 5,720,771 to Snell entitled, "Method and Apparatus for Monitoring Physiological Data From an Implantable Medical Device." The contents of these applications are hereby incorporated by reference as if recited in full herein.

Brief Summary Text (17):
It is also an object of the present invention to provide a dynamic and/or semi-continuous (or even substantially continuous) tumor monitoring system which can be remotely monitored on an ongoing basis during treatment.

Brief Summary Text (18):
It is an additional object of the present invention to provide an implantable cancerous tumor sensor system which is cost-effective and which can provide sufficient ongoing, and preferably substantially real-time, information pertaining to the physiological and/or biological condition of the tumor during a treatment period in a way which provides the information to the physician to assist in therapeutic decisions.

Brief Summary Text (19):
It is yet another object of the present invention to provide a tumor monitoring system which can provide real-time information regarding cancerous tumor physiology as an adjunct to therapy.

Brief Summary Text (20):
It is an additional object of the present invention to provide a cancerous tumor monitoring system which can provide clinically effective regionally specific data representative of the dynamic effects of cytotoxic agents on cell populations during an extended treatment period.

Brief Summary Text (21):
It is another object of the present invention to provide an implantable oxygen sensor configuration which is particularly suitable for monitoring the oxygenation and/or pH level in a tumor.

Brief Summary Text (22):
It is yet another object of the present invention to provide system related sensors and computer program products for identifying when a tumor exhibits potential vulnerability or susceptibility based on data associated with an in vivo in situ sensor which provides measurements of parameters associated with a tumor.

Brief Summary Text (25):
It is still another object of the present invention to provide a system or computer program product for analyzing a plurality of measurements generated by at least one implanted sensor and analyzing the measurements and identifying the presence or absence of one or more predetermined conditions associated with the measurements to alert the clinician of the existence of a potentially vulnerable and desired treatment phase for a tumor.

Brief Summary Text (26):
These and other objects of the present invention are provided by a bio-telemetry based tumor monitoring system with in vivo, in situ sensors positioned to monitor multiple selected parameters representative of the status of a tumor or tumors in a subject.

Brief Summary Text (27):
More particularly, a first aspect of the present invention is a method of monitoring and evaluating the status of a tumor undergoing treatment. The method includes the steps of monitoring in vivo at least one physiological parameter associated with a tumor in a subject undergoing treatment with an in situ sensor. Data associated with at least one monitored physiological parameter is transmitted from an in situ positioned sensor to a receiver external of the subject. The transmitted data is analyzed to determine how the tumor is responding to treatment. Additional data is transmitted and analyzed periodically at a plurality of sequential points in time, and a tumor treatment strategy is evaluated based on the analyzing step.

Brief Summary Text (30):
Another aspect of the present invention is directed to a tumor monitoring system for evaluating the efficacy of radiation or drug treatment and/or identifying enhanced or favorable active treatment windows. The system comprises at least one sensor unit comprising a plurality of sensor elements and associated sensor electronics configured for in vivo, in situ contact with a cancerous tumor in a subject undergoing treatment. The sensor elements are configured to sense a plurality of different physiological parameters associated with the tumor and wirelessly transmit the sensed data. The sensor units have an implanted service life of at least about 6-10 weeks, and more preferably at least about 8-12 weeks. The system also includes a remote receiver in wireless communication with the at least one sensor unit, and is configured to receive the transmitted sensor data. The receiver is positioned external to the subject.

Brief Summary Text (32):
An additional aspect of the present invention is directed to a computer program product for monitoring and analyzing the condition of a tumor undergoing treatment. The computer program product comprises a computer readable storage medium having computer readable program code means embodied in the medium. The computer-readable program code means comprises computer readable program code means for commencing a first wireless data transmission from an in situ sensor with at least one sensor element, where the at least one sensor element is positioned in a subject proximate to a tumor undergoing treatment to monitor at least one physiological or biological parameter of the tumor, and the data transmission includes data corresponding to the output of the at least one sensor element. The product also includes computer readable program code means for commencing a second wireless data transmission from the in situ sensor temporally separate from the first wireless data transmission and computer readable program code means for tracking variation between the first and second data transmissions to provide a dynamic behavioral model of the tumor's response to the treatment.

Drawing Description Text (2):
FIG. 1A is a schematic illustration of a tumor monitoring system according to the present invention. The illustration portrays a real-time monitoring capability.

Drawing Description Text (3):
FIG. 1B is a schematic illustration of an alternate tumor monitoring system according to the present invention. This figure illustrates an ongoing dynamic remote monitoring capability.

Drawing Description Text (4):
FIG. 2A is a schematic diagram of a tumor monitoring system configured to relay real time tumor information during an active treatment session (shown as an electric field treatment therapy) according to one embodiment of the present invention.

Drawing Description Text (5):
FIG. 2B is a block diagram illustrating a tumor monitoring system configured to relay information (real-time) during a hyperthermia and radiation treatment session.

Drawing Description Text (8):
FIG. 5 is a top view of an implantable biocompatible sensor according to the present invention.

Drawing Description Text (9):
FIG. 6A is a top view of an alternative implantable biocompatible sensor according to the present invention.

Drawing Description Text (10):
FIG. 6B is a side view of the sensor shown in FIG. 6A.

Drawing Description Text (12):
FIG. 8A is a section view of the sensor shown in FIG. 7 taken along line 8A--8A.

Drawing Description Text (14):
FIG. 9 is a schematic illustration of an implant sensor according to another embodiment of the present invention.

Drawing Description Text (15):
FIG. 10A is a greatly enlarged cutaway front view of a mock implant of a pH sensor with a pH (ionophore) membrane according to the present invention.

Drawing Description Text (16):
FIG. 10B is a side view of an alternate embodiment of a pH sensor (with iridium oxide).

Drawing Description Text (17):
FIG. 11 is a schematic illustration of an experimental setup used to evaluate an implant tumor sensor according to the present invention.

Drawing Description Text (18):
FIG. 12 is a block diagram of a circuit for an implantable sensor according to the present invention.

Drawing Description Text (25):
FIG. 19A is a schematic illustration of a subject with monitoring system with two separate and spaced apart implant sensors positioned on two different tumors according to one embodiment of the present invention. The monitoring system receiver can refocus to monitor both locations and transmit the data to a remote location.

Drawing Description Text (26):
FIG. 19B illustrates an implant sensor with four sensor elements in position (in situ in vivo) according to one embodiment of the present invention. As shown, two of the sensor elements are positioned at different surface locations on the tumor, while one of the sensor elements is positioned to penetrate a depth into the tumor. Still another of the sensor elements is positioned proximate to normal tissue that is proximate to the malignant tissue or tumor.

Drawing Description Text (28):
FIG. 21 is a photograph of a self-calibrating oxygen sensor.

Drawing Description Text (29):
FIG. 22 is a section view of a self-calibrating combination pH and O.sub.2 sensor.

Drawing Description Text (30):
FIGS. 23A-23C are side views of the sensor of FIG. 22 illustrating a fabrication sequence.

Detailed Description Text (10):
Turning now to FIG. 1A, a real-time tumor monitoring system 10 is illustrated. As shown, the tumor monitoring system 10 includes an in situ sensor unit 50 positioned in a subject 20 proximate to a tumor 25. Preferably, as is also shown, the sensor unit 50 includes a plurality of sensor elements 51 positioned at different locations on and/or into the tumor 25. It is preferred that the sensor elements 51 monitor more than one physiological parameter or a selected physiological parameter associated with the tumor at more than one position in, on, or about the tumor as will be discussed further below. The sensor unit 50 is configured with a telemetry

link 60 to wirelessly communicate with an externally located receiver 75. The receiver 75 includes a computer interface 76 and is operably associated with a physician interface module 80 such as a display monitor associated with a central processing unit, computer, or other computer means to allow physician access to the monitored data. As shown, the physician interface 80 is a laptop or other mobile/portable computer means to allow a physician instant access to the substantially real-time monitored tumor parameters.

Detailed Description Text (13):
FIG. 1B illustrates an alternate embodiment of a tumor monitoring system 10'. In this embodiment, the tumor monitoring system 10' includes a home receiver unit 75' and a remote interface 78 which communicates with the physician interface 80 (the physician interface shown in this embodiment is a central processing unit). The patient 20 (the dotted line represents the patient being in the house proximate to the receiver 75') even when at home can continue to monitor and transmit data to a remote site. The remote interface 78 can provide the communications link between the monitored local data and a remote clinical oversight station. As such, the remote interface 78 can be provided by any number of interface or data load means including a computer modem, a wireless communication system, an internet connection, or telephone connection. In this embodiment, upon identification of the existence or onset of a favorable condition for treatment, the central processing site can automatically schedule an evaluation appointment or even schedule a treatment session on therapeutic equipment to take advantage of an opportune or favorable treatment window(s).

Detailed Description Text (14):
FIG. 3 illustrates a preferred tumor monitoring and treatment evaluation method according to the present invention. At least one (and preferably a plurality of) physiological parameter associated with a tumor in a subject undergoing treatment is monitored (Block 100). Data associated with the at least one physiological parameter is transmitted from an in situ positioned sensor unit 50 to a receiver 75 located external to a subject (Block 110). The data transmission can be remotely transmitted from a non-clinical site (such as at a patient's home) to a clinical site via modem, telephone, wireless communication systems, and the like (Block 115). The transmitted data is then analyzed to determine a condition of the tumor (Block 120). The monitoring, transmitting, and analyzing steps are repeated at a plurality of sequential points in time (Block 125). That is, as opposed to a "static" single point in time data point, the instant invention allows dynamic monitoring (a plurality of sequential points in time). The dynamic tracking to variation in the tumor can yield valuable therapeutic and diagnostic information. The data is transmitted on a periodic basis (such as every 4-24 hours) over a particular treatment period. The data is transmitted in an at least an intermittent manner (although the data may be transmitted in less or more frequent data transmissions) during an entire treatment cycle, typically from about 1-3 months. More preferably, the data is substantially continuously or semi-continuously monitored (every 1-60 minutes, and more preferably every 1-30 minutes) and, at least locally, transmitted. This ongoing (intermittent, semicontinuous, or substantially continuous) monitoring allows the dynamic tracking or monitoring of the physiological parameter(s).

Detailed Description Text (16):
In an alternative embodiment to the home-based tumor monitoring system 10' shown in FIG. 1B, the receiver 75' can be configured to be portable and sufficiently, light weight to allow a user to wear it (attached to clothing or other supporting belts or suspenders or the like) such that it is in a desired proximity to the imbedded sensor unit(s) 50 to more easily provide semi-continuous or substantially continuous dynamic data tracking. Preferably, the portable receiver unit (not shown) is self-powered with a trickle charger (to plug into a vehicle accessory power source or a wall outlet in the home) to allow a user to recharge the unit when not mobile. It is also preferred that the portable unit be configured with

sufficient memory to be able to store a block of data over a period of time before uploading to the remote interface, or directly to a computer interface at a clinical site.

Detailed Description Text (24):
Accordingly, in one embodiment of the present invention, the sensor unit 50 (whether self-powered and implantable or injectable with an inductive powered version as will be discussed further below) can be inserted into the tumor(s) and secured therein or thereto in order to gather information, preferably for a number of weeks as discussed above. As shown in FIG. 19B, the sensor elements 51 are configured such that they are placed at different levels and in different locations in the tumor. It is also preferred, as is also shown in FIG. 19B, that at least one sensor element be configured to monitor the treatment toxic affect or normal cells and/or the pH level of the normal cell tissue proximate the tumor.

Detailed Description Text (25):
It has been shown that a difference in oxygen levels exist between tumor feeding arterioles (about 32 mm Hg) as opposed to the about a 50 mm Hg level in healing or normal tissues. And as noted above, low oxygen levels leads to treatment resistance in a tumor cell. If it is determined, with the aid of the device, that the majority of the tumor is hypoxic (i.e., less than 50 mm Hg, and preferably less than about 40 mm Hg, and more preferably about 32 mm Hg or less), then it should not be treated until the oxygenation of the tumor is improved. This can occur in several ways. The tumor can be heated (hyperthermia) which works best in hypoxic conditions and which may eliminate enough cells to make the remaining population less hypoxic, or the tumor can be exposed to specific drugs to improve the oxygen concentration. The important point is that the tumor is not treated until more cells are oxygenated and, therefore, more sensitive or vulnerable to the conventional active treatments of radiation or chemotherapy. Similarly, the sensitivity and, therefore, cell kill of malignant cells can be affected by pH and cell proliferation. pH measurements of the tumor tissue would be important as the pH can influence not only the delivery and uptake of drugs, but also affect the oxygenation of the tumor. Therefore, if it is determined that the pH of particular tumor is 7.2 and the uptake of the drug of choice is undesirably affected by a pH greater than 6.9, then the drug should be withheld and the pH changed. Cell proliferation can be measured with the aid of a beta radiation sensor able to monitor uptake of any radioactive tagged substance or ligands and provide information on cell kinetics and proliferation. If the uptake of a particular ligand which measures for cell proliferation is high (indicating active cell proliferation and therefore increased sensitivity), then the drug or radiation should be delivered.

Detailed Description Text (27):
Thus, in a preferred embodiment, the present invention configures a tumor monitoring system with sensor elements designed to monitor one or more of tumor pH, oxygenation level, temperature, and cell proliferation. The cell proliferation can be measured presently by the use of a radiation sensor (which can also be used to verify the dose of radiation received at the tumor during radiation therapy). It is anticipated that other biochemical or biomolecules will be determined to be sensitive indicators of the vulnerability of the tumor for treatment and, thus, useful according to the present invention. The present invention can provide all these sensors in each tumor, gathering and transmitting the information in real time, to a computer containing an algorithm to process the information to determine if and how the patient is to be treated.

Detailed Description Text (29):
Similarly, a range of physiological parameter values particular to the parameter can be used as a basis for test criteria; for example, defining the levels associated with "elevated," "decreased" and "normal" can be input (Block 210). This criteria (as well as relative levels, population norms, or other indices of tumor behavior and treatment efficacy) can then be used to define test conditions

corresponding to evaluation of tumor treatments (Block 220). That is, the test conditions can be any number of tests representing evaluation of the tumor and the treatment. As shown, the test conditions also test for abnormal values of the monitored parameters (Block 231). This can identify the malfunction of a sensor, sensor element, or other component of the monitoring system as well as identify a potentially immediate need for medical evaluation. Other test conditions can include testing for elevated or decreased parameter values (Blocks 232, 233) respectively. Similarly, the presence of a clustering of "favorable conditions" represented by two of the parameters having increased or elevated parameter values and another having a decreased parameter value (Block 235) may represent a more favorable treatment period. For example, the presence of an elevated oxygenation level together with a period of increased cell proliferation and a decreased pH level may trigger a favorable treatment window. Of course, the clustering of just the two increased parameters can also be a test condition. In addition, one test condition can review the parameter values to determine variation from an expected value based on a predictive model (statistically relevant variation from a relative reaction or from a population norm) based on a point in time during or after active treatment (Block 234). A test condition which identifies whether the parameters meet the defined desirable values may also be helpful (Block 236). It may also be beneficial to have a test to determine if an expected data monitoring (local and/or remote) has been received or is missing (Block 237). This could indicate data corruption, file corruption, or even be used to automatically call the subject (such as with a programmed or recorded telephonic message) to notify them that a data transmission is needed.

Detailed Description Text (30):
In any event, the physiological data is periodically monitored (Block 240) and the data is compared to the test conditions/defined values (Block 250). An unfavorable active treatment time and a favorable active treatment time can then be identified (Blocks 260, 261), respectively. Of course, other evaluations and therapy decisions can also be made. The favorable test time can be identified by the test conditions/parameter values indicating a positive indicator (favorable condition or good progression). Of course, the data may also reflect a norm indicator (neutral condition), and a negative indicator (unfavorable condition or resistance to therapy). It is envisioned that a global network database or a regional database associated with each hospital or clinical site identifying the appropriate values can be pre-established to minimize-the data input needed for a particular subject.

Detailed Description Text (48):
It will be appreciated by one of skill in the art that when a foreign object is implanted into the body, a series of host responses occur: 1) deposition of blood plasma proteins, 2) fibrin formation, 3) assault by immune cells and proteins, 4) attack by inflammatory cells, and 5) formation of a cellular capsule around the object (Reichert et al., 1992). Therefore, it is important that the materials used in an implanted device address this host response. Much is known about the implantation of sensor systems. Kapton.RTM. polymers have been shown to be relatively benign when used as a sensor substrate (Lindner et al., 1993). Pacemaker companies frequently use titanium cases with medical grade epoxies and silicone rubber to encapsulate the external lead connections (Webster, 1995). Implantable glucose sensors have been constructed using polyethylene cases covered in Dacron velour, with the sensor surfaces being coated with a variety of bioprotective membranes (Gilligan et al., 1994). (These units were wet sterilized in 0.05% thimerosal for 24 hours before being implanted and tested in vivo for up to three months.) A more common method used for sterilizing implant devices is gas sterilization at temperatures of 115.degree. C. to 120.degree. C. for 20 minutes.

Detailed Description Text (58):
Biotelemetrics (Boca Raton, Fla.) builds transmitters whose carrier frequency is adjustable, which makes it possible to stack a series of single channel transmitters to make a multi-channel unit. The size of a typical unit is

approximately 2.5 mm.times.7.5 mm.times.10 mm. The transmitters can be turned on and off periodically to reduce the power consumption. The electronics exhibits a high input impedance which enables the unit to be connected to any kind of sensor (e.g., thermistors, pH sensors, and other ion-selective sensors).

Detailed Description Text (63):
Some preferred sensor embodiments of the present invention are illustrated at FIGS. 5, 6A, 8, 9, and 22. Generally described, the in situ sensor units 50 of the present invention are configured to be one of implantable or injectable into the subject. FIGS. 5, 6, 21, and 22 illustrate preferred implantable embodiments, while FIG. 8 illustrates an injectable embodiment. FIG. 9 illustrates a hybrid sensor unit 50" having both an implantable satellite sensor body 50S and associated injectable dependent sensor bodies 50D. Each of the sensor units of the present invention are powered either by a battery (FIG. 5), or, and more preferably, is inductively powered (FIGS. 6A, 8, and 9). Each of the (implantable or injectable) sensor unit bodies is hermetically sealed with biocompatible materials and sterilized by methods well known to those of skill in the art.

Detailed Description Text (64):
As shown in FIG. 5, the sensor unit 50' is configured with at least one sensor element 51. The sensor element 51 shown in FIG. 5 is a thermistor. More preferably, as shown in FIG. 6a, the sensor unit 50 comprises a plurality of sensor elements 51a-51e, which are preferably configured to monitor one or more of temperature, radiation, oxygen, and pH. Suitable discrete pH, radiation, and temperature elements 51a-51e are known to those of skill in the art. The preferred temperature sensor type is a thermistor. The preferred radiation sensors are well known such as MOSFET (metal oxide semiconductor field effect transistor) based designs. Preferred self-calibrating oxygen and combination oxygen/pH sensor embodiments will be discussed further below.

Detailed Description Text (65):
The temperature sensor element for the present invention is configured to operate in the temperature range of about 35.degree. C. to 45.degree. C. with an accuracy of about 0.1.degree. C. Size is of major importance since the entire implantable device should be minimally invasive. Preferably, the entire implantable sensor unit is sized to be less than about 1.0 cm.sup.3. Further, the sensor units 50, 50', 50" of the tumor monitoring system 10 are configured to operate even when exposed to a radiation field. That is, the sensor unit 50, 50', 50" do not necessarily have to function while the radiation is being administered to the tumor, but they preferably function immediately afterward. The sensor unit 50, 50', 50" is thus configured to respond quickly (within a few seconds) after radiation administration. In a preferred embodiment, as shown in FIG. 8, the sensor unit 50" is sized and configured such that it can be placed on the tip of an insertion probe and injected via a large bore canula such as via image guide placement into position. Referring now to FIGS. 6A and 6B, a preferred embodiment of a sensor unit 50 is shown. The sensor unit 50 is configured with a primary body portion 50B and a plurality of arm portions 50A extending outwardly therefrom. As shown in FIG. 6B, the arms 50A have a thin planar profile. Preferably, the arms 50A are formed of a flexible biocompatible substrate material such as a polyimide (like Kapton.RTM., a polyimide material). At least one sensor element 51 is positioned on each arm 50A, preferably at a distal portion (away from the primary body 50B). A separate channel 151 electrically connects the sensor element 51 to the electronic operating circuitry 125 positioned on the primary body 50B. Of course, a plurality of sensor elements 51 can be positioned on each arm, each with a separate electrical communication channel 151. Preferably, each channel is defined by a pair of leads (the sensor O.sub.2 may have greater than two (2) leads) formed by metal vapor deposition onto the top surface of the flexible substrate.

Detailed Description Text (67):
As shown in FIG. 6B, a biocompatible coating 160 is applied (to preferably

encasulate, and more preferably, hermetically seal) to the exterior of the sensor unit 50. Surface mounted electrical components can also be located on the bottom surface of primary body 50B, with interconnection being made by plated through vias (a common method used in flexible printed circuit board technology). Advantageously, this multi-arm configuration can provide increased regional data to allow for more informal analysis of the tumor. As discussed above, the multiple sensor elements 51 can contact different locations within (penetrate at different depths) and/or wrap to contact different exterior perimeter locations along the tumor. Alternatively, one or more arms can be attached to normal tissue to provide information regarding the status of same. In any event, the sensor arms 50A are preferably configured with attachment means 150 to secure their position in the subject. For example, sensor element 51A illustrates an aperture 150 formed in a distal position of the substrate to allow a suture to attach it in position. Alternatively, sensor element 51b illustrates a barbed outer surface 150'.

Detailed Description Text (68):
FIGS. 7, 8A, and 8B illustrate a sensor unit 50" which is cylindrically shaped and sized for injection, e.g., an injectable sensor unit 50I. In this embodiment, a PCB or IC chip 125p is oriented to extend a small distance along a length of the sensor body. The coil 58 also cylindrically extends to surround a portion of the PCB or IC 125. In the embodiment shown, the PCB is a substrate (preferably a flexible substrate) which extends a distance outside the coil 58 (for an overall length which is less than about 0.5 inches). Of course, with the use of an IC configuration, this size can be further reduced. In addition, the IC or PCB can be configured and sized to extend substantially the same distance as the coil 58. The sensor body can be configured to hold a single channel (i.e., one sensor element for a PCB version having a width of about 3 mm) or multi-channel (multiple elements, with each channel layed side by side, and typically wider than the single channel version). The tip 125T of the sensor unit 50I can be configured with a rounded or pointed edge to help facilitate entry into the tumor tissue. Again, the entire sensor body is encapsulated with a biocompatible material and sterilized for medical applications.

Detailed Description Text (69):
Preferably, both the injectable and implantable versions 50I, 50, respectively, of the sensor units of the present invention, such as those shown in FIGS. 6 and 7, are inductively powered. That is, the monitoring system is configured to act as a transformer (with one coil on the surface of the patient's body and the second within the monitor) to couple and power the internally disposed sensors, as is well known to those of skill in the art and discussed briefly above. As such, the in situ sensor units 50, 50', 50", 50"' are self-contained, and have a sufficiently long service life in the body to provide clinically useful chronic information for episodic or chronic treatment decisions, and can be miniaturized without requiring catheters or externally connected wire leads into the sensors and out of the body.

Detailed Description Text (71):
It will be appreciated that to further miniaturize the device, the temperature sensor resonant element can be configured as a positive temperature coefficient (PTC) (typically ceramic). Although most conventional devices employ NTC (negative temperature coefficient) versions, for the instant application, the PTC may be advantageous.

Detailed Description Text (72):
FIG. 9 illustrates a hybrid sensor unit 50'" version of the inductively powered implantable and injectable sensor units 50, 50I described above which allows for miniaturized sensor element bodies and useful signal strength at transmission. As shown this sensor unit 50'" embodiment includes a satellite sensor unit 50S with the IC or externally communicating electronics 125 thereon and a plurality of dependent sensor units 50D. The dependent sensor units 50D are inductively coupled to the satellite sensor unit 50S which is, in turn, inductively powered and coupled

to the external system. Further, the dependent sensor units 50D are telemetrically connected 60I to the satellite sensor units 50I, which is telemetrically connected 60 to the external receiver 75. Because the dependent sensor units 50D are locally positioned relative to the satellite sensor unit 50S, the signal strength demands are reduced, thereby allowing the injectable sized dependent sensor units 50D to be further reduced in size. Preferably, each dependent sensor units 50D, can be electronically encoded or identified or positionally related to a particular channel or port within the satellite sensor unit 50S to maintain relative (if not absolute) positional information for consistent data analysis of the transmitted sensor data for the monitoring system 10.

Detailed Description Text (73):
FIG. 19A illustrates another embodiment of the present invention, at least one wherein the tumor monitoring system 10'" employs a plurality of sensor units 50. That is, at least one sensor unit 50 is positioned at a different (separate) tumor site as shown. This multi-sensor unit tumor system 10'" can result in more regional specific information to adjust treatment as necessary to effective in each tumor site of concern. Preferably, the multi-sensor monitoring system 10'" will configure each separate sensor unit 50, 50", 50"' to be electronically identifiable to maintain data integrity and correlation to the tumor site/particular location. This can be provided by configuring the receiver 75 and the separate sensor units 50 (50I and 50S/50D) with port communication protocols to identify and/or maintain the relative order of transmittal to the location or position of the particular sensor unit 50 within the body (i.e., channel one for "sensor 1," channel 2 for "sensor 2," each alphanumeric identifier being manually or programmably set at insertion or position onto the tumor in relation to its left to right or up to down position to a relational axis). As the receiver 75 should be positioned proximate to the sensor unit coil 58 (typically about 30 cm) for proper data transmission, it is preferred that the receiver 75 be configured to move to overlay the appropriate sensor unit during transmission (indicated by the arrow and dotted line movement of the receiver in FIG. 19A) and it is also preferred that the receiver 75 be programmed to recognize the order of sensor unit transmission to assure data integrity. Of course, two receivers can be used, one for each sensor unit location. This may be especially appropriate for non-clinical use, such as at a patient's home wherein a patient interactive system may be needed. Thus, a dual receiver configuration, whereby a user can keep in position a portable receiver over each monitored tumor site, can be advantageous.

Detailed Description Text (74):
Of course, an external mark or indices of alignment to allow proper alignment may also be helpful (both in a single tumor/region sensor unit embodiment and a multi-sensor unit/spaced position embodiment). This can be a semi-permanent physical mark 175 made on the skin and/or other infrared or photogrammetric position readable or indication means which can cooperate with the receiver 75 (receiver loop) such that the receiver 75 can send out a position verification beam to facilitate proper alignment before/during transmission at the selected location.

Detailed Description Text (75):
For remote transmissions, the tumor monitoring systems of the instant invention are preferably configured to transmit information at a low or very low bandwidth. That is, the carrier bandwidth is preferably in the MHz range while the modulation frequency is more preferably at or below about 1 kHz. This low bandwidth operation allows transmission of signal data received from the sensors across slow communication links such as modem and voice telephone connections. Preferably, the measured signal information is encoded into one of several time-based modulation schemes. The time-based encoding permits accurate data transmission across communication links that may convey amplitude information inaccurately and frequency information accurately, such as the voice telephone network. In addition, for home site non-clinical use tumor monitoring systems 10', the monitoring equipment is preferably small and relatively inexpensive or cost-effective to be

set-up and operated at remote locations.

Detailed Description Text (76):
Of course, the low bandwidth operation is not required as the data from the sensor units 50, 50I, 50S can be converted into essentially any number of suitable encoding or transmission schemes that are suitable for remote operations, as discussed above, such as substantially continuous or semi-continuous monitoring with a PC at the remote location and storing the data associated with same with time/date stamps so that a complete data set or data segment/record covering a period of hours, days, weeks, or longer can be gathered and transmitted to the central processing site over one or more discrete relatively short data transmitting sessions.

Detailed Description Text (77):
Of all of the major types of temperature sensors, typically the thermistor is by far the most sensitive. It has a fast response time and a high output for interfacing, and small devices are commercially available. The non-linear response is not critical over the small temperature range in which the sensor will function (typically less than about 10.degree.). Although the interfacing circuits require a current source, the silicon overhead is only a few additional transistors. The device is considered fragile for industrial purposes, but should be amply rugged for this application. Sensor self-heating is reduced since the device operates in a limited temperature range and the current can be small and need not be applied continuously. If a battery source is used, the sensor element is preferably insulated or positioned spatially away to reduce its exposure to heat attributed to the battery.

Detailed Description Text (78):
To validate a tumor sensor design, a single-channel, discrete-component, commercial telemetry unit was purchased (Mini Mitter, Inc., Model VM-FH) with externally mounted thermistor. An experiment was conducted at Triangle Radiation Oncology Services (TROS) by placing the thermistor and transmitter into an agar-gel phantom target, and heating the target in a hyperthermia treatment device (Thermotron RF-8) over the therapeutic range of 37.degree. C. to 45.degree. C. FIG. 2A illustrates the principle of operation of a hyperperthermia treatment with a Thermotron.RTM. device. An eight MHz RF signal is applied between the plates of the machine which causes ions between them to oscillate. These oscillations generate heat by friction, producing uniform self-heating of body tissue. The agar-gel phantom is approximately the size of a human torso and mimics the heating characteristics of body tissue. During treatment sessions with a patient, the skin surface temperature is always monitored. In addition, catheters are normally inserted through the skin surface into the tumor undergoing treatment and its vicinity. During treatment, thermocouple probes are inserted through these catheters to record tumor temperatures as the RF energy is applied. These catheters are left in place in the patient between treatment sessions and are frequently a source of discomfort and infection.

Detailed Description Text (82):
The next task was devoted to designing and building a 4-channel, discrete-component prototype circuit using breadboarding techniques. This circuit utilized four thermistors for temperature monitoring. A block diagram of the circuit is illustrated in FIG. 12. Temperature increases were sensed by the four thermistors 51a-51d in response to a corresponding reduction in resistance. A constant current source driving the thermistors 51a-51d was used to measure the resistance. The amplifier 53 voltage output was proportional to the resistance change. A voltage to current converter 54 attached to the amplifier 53 was used to charge a timing capacitor 56. The time period for the voltage on the timing capacitor to reach a threshold was proportional to the change in resistance in the thermistor 51e, and hence proportional to the temperature change at the thermistor's surface. FIGS. 13 and 14A-14C show suitable operational design for sensor circuits. When the

capacitor voltage reaches a preset threshold, the transmitter 157 sends a signal burst at 1.0 MHz to the coil 58. At the same time, the threshold detection circuit 158 discharges the capacitor 56. At the end of the signal burst, the capacitor 56 is allowed to again begin charging toward the threshold value. If the amplifier 53 voltage is high, a large current is dumped into the capacitor 56 leading to a short charging time interval. If the voltage on the amplifier output is zero, then no current is dumped into the timing capacitor 56. In this case, a small current source was included to ensure that the device is operating properly. This small current source forced the transmitter 157 to send out signal bursts at a large time interval for testing purposes. Longer time intervals indicate lower temperature measurements, while shorter ones indicate higher temperatures.

Detailed Description Text (86):
After passing the functional tests, the test chips were exposed to a series of radiation and thermal tests. First the units were thermally tested using a temperature-controlled water bath as shown in FIGS. 17A and 17B. The IC prototype unit used seven channels for sensor data. Four of the channels were connected to thermistors and the remaining three were connected to fixed resistors. FIG. 17A illustrates that the thermistors caused the channel pulse width to vary by approximately 0.03 ms per 0.1.degree. C. while, as shown in FIG. 17B, the fixed resistor channels varied by about 0.003 ms per 0.1.degree. C. These results are well within the accuracy specifications for tumor sensors according to the present invention.

Detailed Description Text (88):
The thermistor and fixed resistor data in FIGS. 18A and 18B suggest that the increase in pulse width during exposure to radiation is due to changes in the active transistor parameters of the IC. These parameter changes are expected based on the experience of many researchers in the effects of radiation upon microelectronic circuits (NPS, 1997). Therefore, the IC device can be considered as a sensor for the radiation exposure.

Detailed Description Text (89):
Accordingly, a fixed resistor channel can be used to measure total exposure. From calibration data for each implant during manufacture, the initial pulse width for the fixed resistor channel will be known. From statistical data obtained about the behavior of the ICs under radiation exposure (data similar to FIGS. 17A and 17B), the slope of the curve will be known. Therefore, real-time measurements from the fixed resistor channel can be compensated to account for the variation based on the reference fixed resistor and known calibration data to give an accurate indication of the radiation exposure history for the implant. Using this total exposure computation, the temperature reading from the thermistor channels can be corrected mathematically to give accurate temperature reading at any radiation exposure level. That is, radiation damage or exposure can cause IC drift, and temperature drift. This is compared to three parameters: a known fixed resistor value which is constant, a temperature sensor value which varies only in response to temperature, and the IC which is affected by both (thermal and radiation). Use of the calibration data established at setup (or in the factory) can calibrate the signal data based on the number of known parameters to determine the radiation based drift and adjust for same. This drift is correctable as the dose of radiation is well within the drift adjustment as indicated by the FIGS. 17 and 18. In operation, a computer means can computationally perform the correction based on the data it receives from one or more fixed resistors.

Detailed Description Text (90):
Accordingly, it is preferred that at least one fixed resistor 125R be used in the operating circuitry of the sensor, and preferably a plurality of fixed resistors. FIG. 14B illustrates one fixed resistor channel (one reference) and four active monitoring channels. In one embodiment, the sensor unit 50 includes three resistors, one is substantially invariant with temperature or radiation (the fixed

resistor 125R), one changes with temperature (a thermistor), and one changes with both temperature and radiation (typically the MOSFET's in the chip have a resistance that changes with both). The thermistor has an associated measured temperature dependent curve. The fixed resistor can be used to correct the bias on the MOSFET'S (adjust or compensate for their drift due to radiation exposure/damage). The computer can give a corrected reading such as a temperature profile.

Detailed Description Text (92):
In order to assess biosurvivability and biocompatibility, several mock implant devices were fabricated using materials that are similar to the preferred embodiments of the sensor units described above. The overall scheme for fabricating a mock implant is highlighted in FIG. 5. The substrate 120 can be fabricated using five-mil flexible Kapton.RTM. polyimide material covered by a 25 micron copper layer. The metal layer 122 is patterned using photolithography into the wiring harness for a simple oscillator circuit. Next, an insulating layer of polyimide can be deposited and patterned to open conducting vias to the metal traces. Then surface mount electrical components 125 are placed and soldered to the substrate. Next, a thermistor 51 is connected to the end branch of the implant substrate as shown in FIG. 5. Then a coil of antenna wire 58 is mounted with the IC and/or SMT components 125 as illustrated in the figure. Finally, a lithium coin-shaped battery 52 is attached to the substrate 120. The battery 52 is first affixed to the substrate in the position shown in FIG. 5. The end flap 129 (the circle that contains the second battery connection) is then folded over the battery and attached using conducting silver epoxy. The entire device is then encapsulated in a biocompatible material such as a thin layer of silastic and/or medical-grade silicone to protect it from the biological environment during implant.

Detailed Description Text (93):
Additional features can also be included in sensor units 50, 50', 50", 50'" based upon the specification of the user interface. For example, the ability to turn the battery on and off with an externally applied RF signal can be included in an IC (chip) design. Another feature can be the inclusion of pH sensor interface electronics. The pH sensors will preferably be implemented on a biocompatible, flexible substrate such as the Kapton.RTM. substrate shown in FIG. 10A (Cosofret, 1995). This design is compatible with the Kapton.RTM. substrate shown in FIG. 5.

Detailed Description Text (94):
In one preferred embodiment, the present invention employs selfcalibrating oxygen, pH, or combination oxygen/pH sensors. The operating principle of the in situ, in vivo self-calibrating chronically implanted sensor units 200, 201, 300 is based on water electrolysis at noble metal electrodes as shown in FIGS. 20 and 22. Oxygen or hydrogen can be evolved by the electrolysis of water by applying a current through a generating electrode ("GE") 227 and counter-generating electrode ("GE'") 227' for a certain period. Accumulation of these dissolved gas molecules at the GE 227, in turn, rapidly establishes a microenvironment of oxygen saturation or hydrogen saturation in close proximity to the microsensor. A two-point calibration procedure for the oxygen sensor unit 200 can then be performed, with the high point calibration being established in an oxygen-saturated phase, and the low point calibration in an oxygen-depleted phase that is produced by saturating the microenvironment with hydrogen. These transient perturbations of the microenvironment are expected to equilibrate rapidly with the surrounding medium (tissue). With this in situ, in vivo self-calibration sensor units 200, 201, 300 periodic sensor calibration can be performed to check the operability and biosurvivability of a chronically implanted device.

Detailed Description Text (95):
It is preferred that the self-calibrating sensor units 200, 201, 300 be configured with the following operational and physical specifications:

h e b b g e e e f c e e ge

Detailed Description Text (101):
The water electrolysis method can be extended to perform a one point, in situ, in vivo calibration of an implanted pH sensor unit 201 (FIG. 10B) as well. A micro pH sensor unit 201 that is surrounded by a generating electrode will experience a titrating pH microenvironment during water electrolysis. If one repeatedly drives the electrolysis current forward and backward through the generating electrode, the highest slope in the time response of the pH sensor will occur at the moment of neutral pH (pH 7.0). Thus, a one-point calibration at neutral pH can be performed during water electrolysis by checking the first derivative of sensor response during titration. The functionality of similar pH titrating microdevices has been demonstrated for a pH-static enzyme sensor or buffer capacity sensor (Olthuis, 1992). This prior work strongly supports the feasibility of one point pH calibration as an option in tumor monitoring applications.

Detailed Description Text (104):
The layout for both configurations were performed using 20, 10, and 5 micron line widths. FIG. 21 is a photograph of the fabricated prototype oxygen sensor 200 (concentric configuration). All noble metal electrodes were made of gold, the material that has been shown to possess the best stability when used as an oxygen catalyzer (Hoare, 1984).

Detailed Description Text (105):
Turning now to the function of each concentric circle shown in FIG. 21, the middle electrode serves as a working electrode ("WE") 225 at which dissolved oxygen molecules are electrochemically reduced. The GE 227 is wrapped around the working electrode; this configuration will establish oxygen-saturated or hydrogensaturated microenvironments during self-calibration cycles. Proceeding from inside to outside, the next concentric circle is used as the reference electrode ("RE") 229. The outermost electrode in FIG. 21 is the counter electrode ("CE") 231 of this three-electrode cell. It is placed as far as possible from the WE 225 to eliminate electrochemical interference at the WE of byproducts generated at the CE 231. The GE' 227' (not shown) is also located remotely from the WE 225 for this same reason. the past, pH sensors have also been fabricated on flexible substrates (Cosfret, 1995). FIG. 10A illustrates a pH sensor structure containing a p-HEMA central dome over a Ag/AgCl electrode. The final fabrication step is the deposition of the outer polymeric membrane containing the pH ionophore. These sensors have performed accurately in preliminary tests in vivo in blood for up to two. months. The size of these potentiometric sensors are preferably minimized to improve their capability for resolving spatial gradients. Further size reduction of the pH sensors shown in FIG. 10A may be limited by the manual deposition of the polymeric membrane solution, weaker adhesion to the substrate and high impedance, as the membrane contact area is diminished. Another drawback imposed by the use of polymeric membranes is the potential for leakage and degradation of membrane's plasticizer and ionophore for long-term operation. More recently, work has been done to miniaturize pH sensors by replacing the polymeric membrane by a solid state analogue. The best alternative identified to date is iridium oxide which has been shown to possess excellent pH-sensing capability and can be deposited on the sensor surface using a simple electroplating method (Marzouk, 1998). This new structure is shown in FIG. 10B.

Detailed Description Text (107):
Another preferred embodiment of an in situ sensor unit is shown in FIG. 22 as a combination pH/O.sub.2 sensor unit 300. As the combination sensor unit 300 assumes smaller feature sizes, the area of the generating electrode and, thus, its current carrying capacity, is reduced. A smaller structure will also enable the new sensors to be employed in linear arrays for gradient measurements. The microenvironment of the smaller sensor may require less oxygen to become saturated. Once the GE 327 has established a saturated microenvironment, these conditions will be dissipated rapidly unless structural measures are taken to delay oxygen and pH equilibration. Hence, the self-calibrating design can employ a recessed structure (a micropool) to

sustain the saturated microenvironment for a limited sensor calibration period. Thus, a 3-dimensional micropool can be configured by using layers of photosensitive polymers to build walls to confine the working and generating electrodes 325, 327. The volume of the micropool can also determine the overall sensor unit 300 performance and the time period needed for calibration. A near optimum design can be determined by iterating several of the design parameters in various fabrication runs. It is noted that some surface degradation and adhesion problems at the polyimide/metal interface at the electrode edges were observed during prototype experiments (at current densities exceeding 10 mA/cm.sup.2).

Detailed Description Text (108):
The conventional Clark oxygen sensor contains a reference electrode (anode) and a working electrode (cathode) located in the same compartment encapsulated by hydrophobic, electrically non-conducting membrane. In contrast, the instant design separates the RE 329 and WE 325 to allow a space for the GE 227 (positioned therebetween and placed to control the micro environment of the WE 225) as illustrated in FIGS. 21 and 22. This new arrangement is in contrast to the conventional Clark sensor, which may not be suitable for long-term implantation due to the risk of membrane rupture and the subsequent degradation of the sensor's internal filling solution. In this design, the separated RE and WE are electrically coupled via a hydrophilic permeable membrane and tissue fluids. This separated configuration for the RE and WE can cause difficulties due to increased solution resistance when the anode is very far from the cathode. However, the 3-electrode system reduces this effect. Another difficulty can be introduced by WE surface contamination due to direct contact with components of tissue fluid that penetrate the permeable membrane. As such, it is preferred that the electrode material used be selected to reduce this behavior. For example, it has demonstrated (Holmstrom, 1998) that a bare gold electrode, implanted up to 4 years for oxygen monitoring, absorbed less blood proteins than a glassy carbon electrode, and no adverse tissue reactions were observed.

Detailed Description Text (109):
To minimize any electrostatic coupling between the 3-electrode cell and generating current source, the operation of the sensor 300 is preferably divided into separate calibration and measurement modes. To simplify the device structure, the counter electrode (CE) will preferably serve a dual as the counter-generating electrode (GE') of generating source. Thus, a single electrode that can be switched between the two operational modes and can serve both functions.

Detailed Description Text (110):
Preferably, to reduce the feature size and reliably form same during fabrication, a silicon wafer-supported flexible substrate process is used to reduce thermal expansions and surface roughness distortions. In this fabrication process, polyimide (DuPont P12723) is spin-cast to a thickness of about 25 .mu.m onto a thermal oxide coated silicon wafer. After all sensor processing steps have been completed, the wafer is soaked in a dilute H.F. solution. The thermal oxide is etched away and thereby releasing the flexible polyimide substrate and its sensor structures.

Detailed Description Text (111):
A recessed sensor structure can also be implemented using photosensitive polymer materials. Thicknesses of up to 30 .mu.m can be obtained with a 2-step spincoating procedure. Other materials are also available for this purpose. For example, a dry film (DuPont Pyralux or Vacrel which have thicknesses of 25 to 100 .mu.m) can be laminated over the device using a thermal vacuum process. The highest aspect ratio (depth:width) for the micropool that can be fabricated using these laminated films is typically about 1:1. This ratio can be maintained for depths from 10 to 100 .mu.m.

Detailed Description Text (112):

h e b b g e e e f c e e ge

Platinum is known as the best noble metal electrode for water electrolysis and is easily deposited and patterned using microfabrication technology. In previous experiments with physiological solutions containing rich chloride ions, surface chloridation of gold generating electrodes was observed during the positive potential region of water electrolysis. This problem should be alleviated by replacing the gold generating and counter electrodes with platinum. For simplicity, in photo-processing steps, a titanium platinum layer will serve as both electrodes and wiring leads. To generate the other electrode surfaces, gold can be electroplated (for the working electrode) and silver (for the reference electrode) onto the platinum layer. For the pH sensor, iridium oxide will also be plated. The devices are designed so that the electroplating steps are self-aligning, and no additional photopatterning will be required. These procedures have already been established (Marzouk, 1998). Currently, the preferred permeable membrane material is p-HEMA covered with polystyrene or collodion (Kreuzer, 1980).

Detailed Description Text (113):
The overall process sequence is shown in FIGS. 23A-23C. Platinum is deposited by sputtering and then patterned by photolithography. Next, a thin layer of polyimide is spin-coated and patterned to define the various electrode areas and to insulate the wiring conductors. Then a thick polymer micropool is defined around working electrode and reference electrode area by a lamination process. Next, gold (as the oxygen catalyzer) or iridium oxide (as the pH-sensitive layer) will be electroplated, followed the plating and chloridation of silver (as the RE). Finally, a permeable membrane is cast by micromanipulation and cured. In operation, it should be noted that with continuous polarizing voltage during oxygen sensor operation, one disadvantage can be a relatively large oxygen consumption and power consumption as well as aging effect. This power consumption is preferably reduced to provide electrode stability. Thus, intermittent or periodic measurement are preferably instituted with a potential step. Necessary calibration parameters such as current density and duration can be determined for proper calibration of periodic measurements.

Detailed Description Text (118):
Following the initial dose of radiation or chemotherapy, each variable will be monitored to determine an appropriate time (associated with a favorable treatment period) to deliver the next dose of radiation and/or chemotherapy. Preferably, each patient is monitored at least four times each day following treatment to establish a specific response pattern for an individual patient. Utilizing this ongoing, periodic monitoring approach can allow delivery of any cytotoxic agent in a more precise and favorable manner and/or to withhold treatment during tumor treatment resistant periods. It is preferably to treat when all variables indicate that the tumor is vulnerable such as when there is an indication of high oxygenation level, low pH, and increased cell proliferation. It the variables do not synchronize to indicate a favorable index at the same time, then a statistical regression analysis can be identified to define an appropriate treatment time. It will be appreciated that in addition to radiation and chemotherapy, hyperthermia and/or other treatments can be incorporated into the treatment protocol, especially in tumors exhibiting a high hypoxic fraction. This can allow for increased cell kill, after which the kinetics of the tumor will change and allow for more precise delivery of the radiation and/or chemotherapy. Thus, the individualized treatment will allow the delivery of cytotoxic agents at a favorable treatment time to achieve increased tumor cell kill, and thereby increase the response of the tumor to the treatment. In this example, when a satisfactory response has been obtained, the tumor can be removed.

Detailed Description Text (128):
Cosofret, V. V., M. Erdosy, T. A. Johnson, and R. P. Buck, "Microfabricated sensor arrays sensitive to pH and K+ for ionic distribution measurements in the beating heart," Analytical Chemistry, Vol. 67, 1995, pp. 1647-53.

Detailed Description Text (136):
Gilligan, B. J., R. K. Rhodes, M. C. Shultz, S. J. Updike, "Evaluation of a subcutaneous glucose sensor out to 3 months in a dog model," Diabetes Care, Vol. 17, 1994, pp. 882-887.

Detailed Description Text (145):
Holmstrom, N., P. Nilsson, J. Carlsten, S. Bowald, "Long-term in vivo experience of an electrochemical sensor using the potential step technique for measurement of mixed venous oxygen pressure," Biosensors & Bioelectronics 13, 1998, pp. 1287-1295.

Detailed Description Text (161):
Olthuis, W., Bergveld, P., "Simplified design of the coulometric sensor-actuator system by the application of a time-dependent actuator current," Sensors and Actuators B, Vol. 7, 1992, pp. 479-483.

Detailed Description Text (162):
Oshima, H., H. Funakubo, T. Dohil, Y. Okabe, T. Katoda, T. Mitsuoka, A. Takeuchi, T. Uchida, "Development of micro-telemetering, multi-sensor capsule system with newly developed LSI for clinical applications," Proc. Int. Conf. on Solid-State Sensors and Actuators, 1987, pp. 163-166.

Detailed Description Text (163):
Puers, B., P. Wouters, M. DeCooman, "A low power multi-channel sensor interface for use in digital telemetry," Sensors and Actuators A, Vols. 37-38, 1993, pp.260-267.

Detailed Description Text (176):
Wouters, P., M. De Cooman, R. Puers, "A multi-purpose CMOS sensor interface for low-power applications," IEEE Journal of Solid-State Circuits, Vol. 29, No. 8, August 1994, pp. 952-956.

Detailed Description Paragraph Table (2):
TABLE 2 Oxygen Sensor Process Process Steps Process Details Substrate 3-mil Kapton .RTM. VN selection Cleaning Organic solvent cleaning and dehydration Metal Deposition DC Magnetron sputtering 200 .ANG. Cr followed by 2000 .ANG. Au Photolithography Spin coated 1.3 .mu.m Shipley 1813 photoresist,. Contact exposure with Tamarack Alignment and Exposure System. (Exposure energy optimized for 5-.mu.m linewidth.) Metal Etching Wet chemical etching Cleaning Organic solvent cleaning and dehydration Polyimide process Spin coated 2-.mu.m Pyralin PI-2721 photosensitive polyimide. Contact exposure with Tamarack system. Spin development and thermal curing in atmosphere

Detailed Description Paragraph Table (3):
TABLE 2 Oxygen Sensor Process Process Steps Process Details Substrate 3-mil Kapton .RTM. VN selection Cleaning Organic solvent cleaning and dehydration Metal Deposition DC Magnetron sputtering 200 .ANG. Cr followed by 2000 .ANG. Au Photolithography Spin coated 1.3 .mu.m Shipley 1813 photoresist,. Contact exposure with Tamarack Alignment and Exposure System. (Exposure energy optimized for 5-.mu.m linewidth.) Metal Etching Wet chemical etching Cleaning Organic solvent cleaning and dehydration Polyimide process Spin coated 2-.mu.m Pyralin PI-2721 photosensitive polyimide. Contact exposure with Tamarack system. Spin development and thermal curing in atmosphere

Other Reference Publication (1):
Cosofret et al., "Microfabricated sensor arrays sensitive to pH and K+ for ionic distribution measurements in the beating heart," Analytical Chemistry, vol. 67, pp. 1647-1653 (1995).

Other Reference Publication (6):
Y. Oshima et al; Development of Micro-Telemetering Multi-Sensor Capsule System with

newly developed LSI for the clinical applications; Transducers '87, The 4.sup.th International Conference on Solid-State Sensors and Actuators; pp 163-166.

Other Reference Publication (29):
Griffiths et al., "The OxyLite: a fibre-optic oxygen sensor," British J. of Radiology, vol. 72 pp. 627-630 (1999).

Other Reference Publication (31):
Mittal et al., Evaluation of an Ingestible Telemetric Temperature Sensor for Deep Hyperthermia Applications,: Int. J. Radiation Oncology Biol. Phys., vol. 21, pp. 1353-1361 (1991).

CLAIMS:

1. A method of monitoring and evaluating the status of a tumor undergoing treatment, comprising the steps of:

(a) monitoring in vivo at least one physiological parameter associated with a tumor in a subject undergoing treatment with an in situ sensor unit;

(b) transmitting data associated with the at least one monitored physiological parameter from the in situ positioned sensor unit to a receiver located external to the subject;

(c) analyzing the transmitted data to determine a condition of the tumor;

(d) repeating steps (a), (b), and (c) periodically at a plurality of sequential points in time; and

(e) evaluating a tumor treatment strategy comprising at least one of:

identifying a favorable or unfavorable tumor treatment time for administration of at least one of a radiation, drug, and chemical therapy;

evaluating the efficacy of at least one of therapeutic radiation, drug, and chemical treatment on the tumor;

determining the amount of radiation delivered in vivo to the tumor site;

monitoring radiolabeled drug uptake at the tumor site; and

analyzing the transmitted data to monitor the influence of at least one of a thermal, chemical, or radiation therapy on the tumor based on data transferred before, during and after the therapy.

14. A method according to claim 1, further comprising the step of positioning at least one sensor unit configured to monitor a plurality of physiological parameters into a subject such that it is positioned in in situ in vivo contact with a target tumor, wherein the positioned sensor unit has a service life of at least about 4-10 weeks.

15. A method according to claim 1, wherein said monitoring step is performed by a sensor unit with a plurality of sensor elements positioned in situ, and wherein said sensor unit is positioned in the subject by at least one of implanting and injecting the sensor unit such that at least one of the sensor elements contacts the tumor.

16. A method according to claim 14, wherein said positioning step comprises injecting multiple discrete dependent sensor units into the subject such that they contact the target tumor and further comprises implanting a satellite sensor unit

in wireless electrical communication with said dependent sensor units into the subject such that the satellite sensor is positioned proximate to said dependent sensor units.

18. A method according to claim 17, wherein the subject has multiple tumors, and wherein said method further comprises positioning a first sensor unit in situ to contact a first tumor and positioning a second sensor unit in situ proximate to a second tumor different from the first tumor.

19. A method according to claim 15, wherein at least one of said sensor elements is configured to monitor the toxic effects of treatment on normal cell tissue proximate to the tumor.

34. A method according to claim 15, wherein said sensor unit includes sensor electronics, and wherein said method further comprises the step of adjusting the transmitted data to account for deviations in the data attributed to the sensor unit's exposure to at least one of radiation and temperature.

39. A method according to claim 1, wherein said monitoring step is carried out via at least one sensor unit having a plurality of in situ sensor elements having a service life of at least about 4-10 weeks, and wherein said method further comprises the step of locally transmitting data associated with the at least one monitored physiological parameter representative of a physiological condition associated with the tumor thereby providing substantially real-time information regarding the condition of the tumor.

42. A tumor monitoring system for identifying enhanced active cancer treatment windows, comprising:

at least one implantable sensor unit comprising a plurality of sensor elements and associated sensor electronics, wherein a plurality of said plurality of sensor elements are configured for in vivo in situ contact with a cancerous tumor in a subject undergoing treatment for cancer, and wherein said sensor elements are configured to detect a plurality of different parameters associated with the tumor and wirelessly transmit data associated with the detected parameters, wherein said plurality of different parameters includes at least two of the amount of radiation exposure at the tumor site, extracellular pH of the tumor, pH of normal tissue, tumor cell oxygenation, tumor cell proliferation and temperature;

a remote receiver in wireless communication with said at least one sensor, said receiver configured to receive the transmitted data, wherein said receiver is spatially separate from said at least one sensor and positioned external to the subject; and

a processor having computer readable program code for analyzing the transmitted data to identify the presence or absence of a favorable cancer treatment condition.

43. A tumor monitoring system according to claim 42, further comprising computer readable program code means for reviewing and adjusting the received transmitted data to correct for variations in the signal data attributed to environmental exposure of the sensor unit or sensors elements held in the subject.

44. A tumor monitoring system according to claim 42, wherein, in position, said plurality of sensor elements are configured to reside at different locations on and within the tumor, and wherein at least one of said plurality of sensor elements is configured to contact normal tissue cells proximate to the tumor.

45. A tumor monitoring system according to claim 42, wherein said remote unit is configured to be worn by the subject, and wherein said remote receiver further

comprises a remote interface to allow a user to transmit data from a physically remote non-clinical site to a central processing unit at a clinical site during a non-emission cancer treatment period.

46. A tumor monitoring system according to claim 42, wherein said sensor unit is configured as a cylindrically shaped body having opposing first and second ends, and wherein said sensor unit includes an inductively coupled power source, wherein said sensor is sized to have a length which is less than about 0.5 inches (1.27 cm) and is configured to be injectable via a trochar into the subject such that at least one of said first and second ends contacts a tumor within a mammalian body, and wherein said at least one sensor unit has an implanted service life of at least about 4-10 weeks.

47. A tumor monitoring system according to claim 42, wherein said sensor unit comprises operating electronics positioned within a first body portion and a plurality of flexible arms extending outwardly therefrom, each of said arms having distal portions containing at least one sensor element thereon and having at least one signal path between said operating electronics in said first body portion to each of said sensor elements in each of said arms.

48. A tumor monitoring system according to claim 42, wherein said sensor unit includes an inductively coupled power source, and wherein at least one of said arms includes a plurality of sensor elements.

49. A tumor monitoring system according to claim 42, wherein said arms are configured with an anchor portion to positionally attach to a desired portion of the tumor.

50. A tumor monitoring system according to claim 42, wherein said sensor elements include at least one pH sensor element, at least one oxygen sensor element, at least one temperature sensor element, and at least one radiation sensor element.

51. A tumor monitoring system according to claim 42, wherein said at least one sensor unit comprises a plurality of sensor elements is configured as an implantable satellite sensor unit and an associated plurality of injectable discrete dependent sensor units, wherein each of said discrete dependent sensor units have at least one sensor element thereon, and wherein said plurality of discrete dependent sensor units are in wireless communication with said satellite sensor unit.

52. A tumor monitoring system according to claim 42, wherein said at least one sensor unit is a plurality of sensor units, and wherein each sensor unit includes a unique identifier to allow transmitted data to be correlated to the appropriate in situ sensor unit position.

53. A tumor monitoring system according to claim 42, wherein said remote receiver is portable and wearable by the patient so as to be held proximate thereto.

54. A computer program product for monitoring and analyzing the condition of a tumor in a patient undergoing cancer treatment, the computer program product comprising:

a computer readable storage medium having computer readable program code means embodied in said medium, said computer-readable program code means comprising:

computer readable program code means for commencing a first wireless data transmission from an in situ wireless sensor with at least one sensor element positioned in a subject proximate to a tumor site undergoing treatment for cancer, the data transmission including data corresponding to the output of the at least one sensor element;

computer readable program code means for commencing a second wireless data transmission from the in situ sensor temporally separate from the first wireless data transmission;

computer readable program code means for tracking variation between the first and second data transmissions to provide a dynamic behavioral model of the tumor's response to the treatment;

computer readable program code for analyzing the transmitted data to identify at least one favorable cancer treatment opportunity;

computer readable program code means for evaluating at least one of (a) the amount of radiation exposure delivered to the tumor site from a cancer radiation treatment session, (b) cell proliferation associated with the tumor, (c) the response of normal tissue proximate the tumor site to the cancer treatment; (d) the value of at least one physiological or biological parameter of the tumor to evaluate efficacy of a cytotoxic or targeted drug or chemical treatment or to confirm delivery of the cytotoxic or targeted drug or chemical treatment to the tumor site, (e) a variation in the value of a physiological or biological parameter of the tumor from a predictive model, (f) the presence of an unfavorable cancer treatment period, and (g) the value of at least one physiological or biological parameter of the tumor to identify a receptiveness for a particular cancer therapy type.